IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Daniel Zamanillo Castanedo	DOCKET NO.:	P03,0588
SERIAL NO.:	10/731,379	ART UNIT:	1633
FILED:	December 9, 2003	EXAMINER:	Kelaginamane T. Hiriyanna
CONF. NO.:	4441		

TITLE: NON-HUMAN MUTANT MAMMALS DEFICIENT IN SIGMA RECEPTORS AND THEIR APPLICATIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Declarant, José Manuel Baeyens Cabrera, hereby declares and states that:

1. I am the inventor of WO 2006/010587, and a faculty member of the Department of Pharmacology at the University of Granada.

2. I have read and am familiar with the specification and claims as originally filed as U.S. Serial No. 10/731,379 on December 9, 2003 (a copy of which is attached as Exhibit A).

3. I have read and am familiar with the Office Action mailed June 28, 2006 (copy attached as Exhibit B); and with the Preliminary Amendment A, filed December 9, 2003 (copy attached as Exhibit C).

4. At my direction, experiments were conducted using Von Frey's model of mechanical allodynia. Such experiments are disclosed in WO 2006/010587 (copy attached as Exhibit D).

5. More specifically, according to the IASP, "allodynia" is defined as "a pain due to stimulus which does not normally provoke pain" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002)). Mechanical allodynia is a form of allodynia where mechanical stimuli cause the painful sensation.

6. The Von Frey model involves the injection of capsaicin into experimental models which produces acute pain followed by allodynia. The mechanisms involved in capsaicin-induced acute pain and allodynia are relatively well known, and mainly include the activation of peripheral nociceptors and sensitization of spinal cord neurons.

7. Figure 1, attached as Exhibit E, shows the test protocol I used to study mechanical allodynia. After habituation, mice were treated with a test-compound (or none for controls). Then, capsaicin (1% DMSO) was injected into paws of the treated mice. Such injection resulted in pain in the effected paw. The effected paw was then treated with a mechanical stimulus, and the latency period before the mouse withdrew its paw was measured.

8. To test the role of sigma receptors in mechanical allodynia, knock-out ("KO") mice lacking sigma 1 receptors were prepared according to WO 2004/52092 (attached as Exhibit F). Such KO mice were tested in comparison to wild-type mice using the Von-Frey model described above.

9. As demonstrated in Figure 4, attached as Exhibit G, for wild-type mice (A), as the dose of capsaicin administered to a mouse increases, the time period before the mouse withdraws his paw decreases (termed "latency period"). However, for KO mice lacking sigma 1 receptors (B), as the dose of capsaicin administered increases, the latency period remains the same.

10. From the results of this study, I have concluded that sigma 1 receptors in the mouse model described above play a role in mechanical allodyina. As a result, KO mice lacking

sigma 1 receptors can be used as a model to study mechanical allodynia, a known disease state in human beings.

11. I further declare that all statements made herein are of my own knowledge and are true and all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that any willful false statements or the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such false statements may jeopardize the validity of this application or any patent issuing thereon.

This is a complete statement of the Declarant.

José M. Baeyens December 13, 2006

José Manuel Baeyens Cabrera Date

CHI\4766894.1